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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,649	10/05/2001	Monica Jonsson	003300-833	2032

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EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/13/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,649	JONSSON ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42,44 and 46-84* is/are pending in the application.

4a) Of the above claim(s) *38-42,44 and 46-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37 and 60-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendments filed May 27, 2003 have been entered.

The addition of claims 60-84 is amendments filed May 27, 2003 is acknowledged.

The outstanding objection is withdrawn in view of the amendments filed May 27, 2003.

The outstanding rejections under 35 USC 112, second paragraph with regards to the expression "under such conditions that the biologically active substance is concentrated and/or solidified", "starch is substantially lacking in covalently bonded extra chemical ... found in hydroxyethyl starch", and the broad and narrow limitations are withdrawn in view of the amendments filed May 27, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-37 and 60-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "highly viscous solution " in claims 1, 3 and 5 is a relative term which renders the claim indefinite. The term "highly viscous solution" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the

scope of the invention. It is not clear what viscosity the solution would have in order to be considered as highly viscous.

The term "reversibly solidified active substance" in claim 4 renders the claims indefinite as to what substance are encompassed by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-37 and 60-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woiszwillo et al. (US Patent 5,981,719 from IDS received January 22, 2002), Ekman et al. (US Patent 4,822,535) in view of Laakso et al. (Journal of Pharmaceutical Sciences, 1986;75(10):962-967 from IDS received January 22, 2002) and Takada et al. (US Patent 5,622,657 from IDS received January 22, 2002), references of record in previous office action mailed February 26, 2003.

Woiszwillo et al. teaches a method of preparing biological active microparticles suitable for parenteral administration by mixing an aqueous solution of bioactive compounds, such as insulin, leuprolide, and bovine Serum Albumin, with the solution of polyethylene glycol. The microparticles are collected after heating to temperature between 37 - 70°C, centrifuging and washing (See col. 21, line 11-34; also col. 5, line 65 - col.7, line 49). Woiszwillo et al. also teaches the biological active substances as enzymes, recombinant proteins, polypeptide, carbonhydrate, such as insulin, leuprolide, and Bovine Serum Albumin (See col. 7, line 50 – col. 8, line 32). Woiszwillo et al. also teaches the concentration of the polymer as between 5-50% (see col. 11, line 48). Woiszwillo et al. also teaches the solution of preferred polymers, including polyethylene glycol, having molecular weight of 3,000 to 500,000 daltons can be added to the solution of the macromolecules in order to form a microparticles (See col. 12, lines 33-

42). Woiszwillo et al. also teaches the way to optimizing the microparticles by altering the particle size and temperature (See col. 13, lines 30-36).

Ekman et al. teaches a method to encapsulate bioactive substance in order to form a solid microparticles by employing a two-phase emulsion system (See abstract, also col. 9, line 13 – 26). Ekman et al. teaches the two-phase system suitable for the preparation of such microparticle as polyethylene glycol/soluble starch/water (See col. 2, line 11-12). Ekman et al. also teaches the drying steps may be accomplished by evaporation or ultrafiltration, in which evaporation would include heating or reduced pressure (e.g., freeze-drying) (See col. 3, line 1-8). Ekman et al. also teaches the polyethylene glycol as preferred polymer and its molecular weight as 100-2,000,000 Da (See col. 4, line 36).

The references do not expressly teach the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. The references do not expressly teach the herein claimed characteristics (i.e., nitrogen content, particle size, and amyloprectin content) of starch employed. The references do not expressly teach the optional steps recited in claims 35-37. The references do not expressly teach the herein claimed temperature employed. The references do not expressly teach the herein claimed concentrations and molecular weight of polyethylene glycol.

Laakso et al. teaches polyacryl starch is suitable as carrier for passive target drug delivery since polyacryl starch is rapidly taken up by the reticuloendothelial system (RES) (see the abstract). Laakso et al. also teaches the nitrogen content of polyacryl

starch can be affected by the amount of initiator employed (See the abstract and figure 2 in page 964). Laakso et al. teaches the degradation of polyacryl starch can be affected by the amount of initiator employed and the degree of derivatization of the starch (See particularly the abstract and page 966-967, Discussion Section).

Takada et al. teaches a prolonged release biological active microparticles which is coated by copolymers of poyllactic/glycolic acid (See col. 7, line 15-53). Takada et al. teaches such sustained release formulation is useful for various peptides and hormones (See col. 3, line 28 – col. 4, line 34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the herein claimed microparticles by employing the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed temperature and particle size in the herein claimed method. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles.

One of ordinary skill in the art would have been motivated to prepare the herein claimed microparticles by employing the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. because Woiszwillo et al.'s method is to prepare a microparticle and then Ekman et al. would further encapsulate such microparticle to increasing the stability of the biological active substances.

One of ordinary skill in the art would have been motivated to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles since the polyacryl starch is well-known as useful for passive targeting drug delivery. Optimizing the nitrogen content, molecular weight, the starch solution concentration, the weight ratio between the biological active substance and starch, the temperature employed, and particle size would be considered obvious as being within the purview of skilled artisan.

One of ordinary skill in the art would have been motivated to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle since such materials are well-known to be useful as sustained release material for peptide medicine. Employing the herein claimed polymer as sustained release shell would have been reasonably expected to be similarly useful.

One of ordinary skill in the art would have been motivated to employ the herein claimed temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles. Optimization is seen to be within the purview of the skilled artisan, absent evidence to the contrary.

Response to Arguments

Applicant's arguments filed May 27, 2003 averring the cited prior art's failure to teach newly recited steps in claim 1 have been fully considered but they are not persuasive. Woiszwillo et al. clearly teaches the addition of polymer solution into the macromolecules solution in order to form the microparticles.

Applicant's arguments filed May 27, 2003 averring the cited prior art's failure to teach the herein claimed characteristics of the herein claimed microparticles have been considered. The cited prior art clearly teaches the every step of the herein claimed method steps of preparing the herein claimed microparticles. Therefore, the cited prior art, as a whole, renders the herein claims obvious, absent evidence to the contrary.

It is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972). In the instant case, the examples disclosed in the specification do not demonstrate the unexpected characteristics of the microparticles. Therefore, the unexpected benefits are not seen to be present herein.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
August 1, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

8/1/03